WHAT IS AGING?*

The Ludwig Kast Lecture†

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To be called upon to deliver this lecture honoring Dr. Ludwig Kast is of particular significance to me. Dr. Kast was a forward thinking man, who, through the Josiah Macy, Jr. Foundation, did much to further the development of research on aging in the United States: This is a matter of record. It is also a matter of record that my first post-doctoral post in 1941 at the Washington University School of Medicine was financed by a grant for research on aging from the Josiah Macy, Jr. Foundation.

One might assume, from the title of my talk, that a firm definition of aging will be offered before I close; the assumption, unfortunately, would not be valid. According to my desk dictionary, "to define" is:

"1. To mark the limits or boundaries of; to make distinct or fix in outline or character.

2. To describe, expound, or interpret; to explain, hence, to determine the precise significance of; to discover and set forth the meaning of, as a word.

3. To set apart in a class by identifying marks; to distinguish."

Any number of maladies of man or beast can be defined in accord with the preceding criteria: diphtheria, poliomyelitis, erythroblastosis, etc. Diphtheria, for example, is defined as:

> "An acute infectious disease or toxicosis due to the presence of *Corynebacterium diphtheriae*. The disease may be attended with patches of false membrane in the throat or on other mucous surfaces and the resulting absorption of diphtheria toxin. The disease is attended with swelling of the larynx and pharynx, and consequent dyspnea, aphonia, and dysphagia. The general symptoms are: fever, heart weakness, anemia, and great prostra-

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tion. Diphtheria continues from a few days to one or two weeks, frequently ending fatally. It is extremely contagious."

This is a definition. The disease is delimited and set apart by identifying marks. A specific causative agent is indicated, the symptoms are listed, as is the time course and prognosis.

How can we do the same for aging? What is the causative agent? When does the condition begin? What are the changes that occur in aging? What is the time course of the disease (if, indeed, aging may be called a disease)? The only point that may be made with assurance is that aging invariably results in death of the organism.

From a less academic viewpoint, the situation is even further confused by a lack of resolution between concern with aging and concern for the aged. The last ten years have seen a phenomenal growth of interest in problems of the aged. Thousands are professionally concerned with the welfare of the elderly and the senile. With the tremendous increase in life expectancy that we are enjoying today and is mushrooming steadily, our entire population structure stands to be altered sharply. Thanks to the conquest of infectious diseases more of us are living long enough to experience cardiovascular diseases, malignancies and senile decay. Medicine is increasingly concerned with problems attending care of the aged patient.

With more of us living long enough to enter into post-compulsory retirement life, there is ever-growing concern by social scientists and economists in annuities, retirement schemes and Social Security systems. Still others press for extension of retirement age or abolition of compulsory retirement. Entry into retirement usually signifies the beginning of a period of intense insecurity. Finances are inadequate; modern transport has spread families over hundreds and thousands of miles so that the retired person or couple cannot readily move in with children. Even if the children do live nearby, modern housing is not designed to accommodate the presence of old folks in a dwelling. The feeling of being un-needed and unwanted grows. It is into this breach that the social workers attempt to step.

All of these problems that have been listed are real and severe, but they are problems of the aged. When it comes to problems of aging, the strategic rather tactical problem, the academic issue, the questions of what is aging, why is aging, what are the changes that occur during aging, it is painful to note that there are less than a handful of serious

workers in this field in the United States.

There are probably a number of factors responsible for the paucity of basic scientists in research on aging. Funds for research are more readily available for research on diseases of popular concern, but I do not believe that there is a serious shortage of funds for research on aging. More likely than not, the lack of clues that might direct research into specific avenues is primarily responsible. An appreciation of the apparent inevitability of aging no doubt dissuades many from dabbling in this problem.

I have already taken the view that a sound definition cannot be formulated now. It may also be noted that there is a surprising lack of variety insofar as theories of aging are concerned. Let us omit from our discussion the frankly irresponsible and imaginative notions that crop up from time to time, the "fountain of youth" sort of thing. Not much will be missed if, in addition, we omit discussion of the theory of auto-intoxication resulting from intestinal putrefaction. Metchnikoff[1] was seriously taken by this notion at the turn of the century, and although it more or less faded after Metchnikoff's death, every now and then a paper appears urging that intestinal putrefaction is the cause of aging. The same objection that applies to the theories that aging results from failure of the cardiovascular system, or nervous system, or failure of any particular mammalian organ, also applies to the intestinal intoxication theory. I have stressed repeatedly, and will continue to stress, that aging is too fundamental a process to be rationalized so simply. Aging is virtually universal. It occurs in plants as well as in animals. It occurs in animals without arteries, without large intestines, and without complex nervous systems. Even in these relatively simple animals the process of aging follows a pattern much like that of man. The organism develops, goes through a brief adolescence, matures, enjoys a brief period of adult vigor, gradually declines, and dies.

To be taken seriously is the concept that senescence is due to the failure, or deterioration with time, of the protoplasmic colloids. Among the early proponents of this theory were Dhar and Marinesco. A parallel is drawn between the *in vitro* aging of colloids as manifested by syneresis, and the apparent loss of water from *in vivo* colloid systems. Similar in principle, but put more simply, is the often expressed thought that aging is like the running down of a clock, the wearing out of an automobile part or a pair of shoes. The difficulty with this whole con-

cept is that the living cell is not a clock, not an automobile motor, nor a pair of shoes. The latter are non-living systems—they do not possess a self-synthetic mechanism. The living cell does. A critical, diagnostic feature of the living system is the capacity for self-renewal. It is an expression of this capacity for self-renewal that is measured in turnover studies with radioactive isotopes. Protoplasmic constituents are constantly being replaced albeit at varying rates. If, in senescence, there are "old" protoplasmic constituents present, it can only be due to inadequacy of the self-synthetic mechanism. Indeed, it is not too far-fetched to speculate that aging is primarily due to an insufficient rate of protoplasmic self-duplication.

One last general group of theories on aging remains to be considered. Although they vary in detail, all hold in principle that in senescence there is a progressive accumulation of toxic materials in the cell. These materials, whether they are held to be pigments, crystals, insoluble compounds, or products of incomplete metabolism, are supposed to interfere with vigorous cellular life. Some decades ago, Benedict refined this concept by proposing that in senescence cellular permeability is decreased. More recently, I espoused this idea and elaborated it still further by proposing that the decrease in cell permeability is a product of an increase in the calcium content of the cell surface.[2] Aside from the fact that there is little evidence that cell permeability does decrease with age, these theories leave us in much the same quandary as we would be without them. Why should permeability of the cell decrease with age? Or, if calcium does increase with age to decrease transport across the cell membrane, why should this happen? One is taken back to my earlier suggestion that aging may involve inadequate self-duplication, in this case referring specifically to inadequate renewal of the cell surface.

Thus far I have emphasized the things that we don't know. Perhaps I have been too gloomy. There are some observations that could well serve as take-off points for further experimentation.

First, I have in mind a relatively uncommon clinical situation known as progeria. In this disease of children there is the appearance of many of the superficial characteristics of senility. Although abnormal adrenal and anterior pituitary glands in the victims of progeria might point to an endocrine disturbance, the suggestion of premature senility is strong. As a matter of fact, many of these children die of coronary thrombosis. It may well be that the association between progeria and senility may be

little more than a figment of the imagination. On a long chance it may also be that a profound metabolic disturbance does bring about premature senility in these children. A comprehensive analysis of the clinical and histological changes in such individuals might be rewarding.

Returning to tissues and cells one comes to the liver, the happy hunting ground of biochemists and histologists. There have been a few studies of the nucleic acid content of young and old liver cells. One might expect a quantitative reduction in either or both pentose and desoxypentose nucleic acid in old cells. Nucleic acids are thoroughly established as associated with protein synthesis. Old tissues presumably are less capable of protein synthesis and, hence, should contain less of these materials. However, Lowry[3] and, later, Schulz[4] found no significant change with age in the amount of either of the two nucleic acids. It may well be that the methods employed were not sufficiently subtle to detect fine differences or it may well be that the physical structure of the nucleoproteins change with age rather than their amount per cell. Certainly, the old liver cell is not as effective as the young. Mitotic activity in regenerating old liver is lower than that of young liver. Also, the P^{32} uptake of old liver after experimental hepatectomy is reduced. McKellar's[5] cytological analysis of rat liver is also interesting. During fetal life there is, of course, a high level of mitotic activity. This means that both chromosomes and nucleus are dividing along with the cytoplasm. Later, in the young animal one finds an increasing number of binucleate cells along with the products of normal mitosis. In this situation it would appear that while the chromosomes and nuclei are dividing in synchrony, the cytoplasm is not. Still later, in middle life polyploid cells increase in population density, indicating that while chromosomes are multiplying both the nucleus and cytoplasm are lagging. This progressive failure of capacity for multiplication may be taken as a measure of reduced growth potential.

This is my thesis—aging is a product of reduced growth potential. It is a restatement of my earlier suggestion that aging must be a consequence of inhibited capacity for self-duplication. There is evidence to support this view. Nothing would please me more than to review these data in detail. Yet, out of consideration for my audience I will be most concise. Biologists studying senescence are few and the data are slow in accumulating. One is compelled, as I have been, to cite the same works over and over again.

Chronologically, Sonneborn's[6] experiments of 1930 come first. Although he was not particularly interested in gerontology at the time, his observation on the flatworm, Stenostomum incaudatum, represents one of the major advances in the field. His experimental animal, Stenostomum, was presumably genetically homozygous and was raised under standardized conditions. Reproducing asexually, Stenostomum multiplies by transverse fission to give rise to anterior and posterior daughter organisms. These two differ in one significant respect; the anterior product receives the head and much of the trunk of the dividing mother and has only to regenerate the tail component to be complete, while the posterior product of transverse fission must regenerate a full head and much of the trunk.

Thus, the anterior daughter experiences little cell multiplication and growth while the converse is true for the posterior daughter. In the design of his experiment, Sonneborn segregated these fission products in isolation cultures and established two contrasting lines of purely anterior or posterior products through a series of generations. Bearing in mind that all the lines were genetically uniform and nurtured under standardized environmental conditions, one might expect comparable life spans for all of the lines. This was not the case. The mean length of life in days for all of the anterior lines studied was 35.0 ± 1.1, while four posterior lines had a mean life span of 63.5 days, two lived 77.0 days and the last two lines had lived 115.0 days, at which time the lines were discarded. It would appear that lack of active growth in the anterior lines is coupled with the observed reduced longevity.

Several years ago, I made a comparable series of observations on a multicellular but microscopic fresh water organism, the rotifer.[7] The rotifer's development is determinate; all of its cells are formed during embryonic life and, hence, are of the same age. In addition, since its reproduction is parthenogenetic, all the reproductive products of an individual are genetically identical. Using a standardized culturing technique, I attempted to determine if the progeny of actively growing, adolescent rotifers have different life spans than progeny of full grown and elderly mothers.

As in Sonneborn's experiments, two types of divergent lines were established. One was composed of successive generations of first born rotifers; the other consisted of successive generations of descendants of full grown or elderly mothers. In the lines of rotifers derived from

adult mothers the mean life span decreased in each successive generation until the line became extinct, and the number of generations required to bring a line to its end depended upon the age of the mothers. Lines derived from elderly mothers died out in four generations, from middle-aged mothers died out in eight generations, and from newly matured mothers in seventeen generations. Apparently a capacity for reducing longevity is transmitted through adult rotifer eggs. This does not occur in lines of rotifers from actively growing adolescent animals. Longevity of each successive generation is greater than that of the preceding, so that in experiments carried through 54 generations rotifers were developed whose longevity was four times greater than that of the original stock. The eggs of actively growing rotifers do not contain, or at least do not express, the capacity for reducing longevity. There were a number of interesting ramifications to these experiments, but they are not essential for this discussion. One intriguing question does come up. How does one reconcile these observations with Weismann's concept of the immortality of germ-plasm? If our observations are sound, it would appear that the germ-plasm of the adult of at least one species is as mortal as its somatoplasm. Perhaps the concept should be modified to this extent; the germ-plasm of only the actively growing young individual is potentially immortal and perpetuates the species. It may even be that aging of a species results from conditions favoring breeding of adult and elderly individuals.

We still have not defined aging. Can we at least develop a reasonable description of the process? Aging certainly is not advantageous from the point of view of the individual, it always has a fatal outcome, time is of the essence. Lastly, aging occurs when growth slows down or stops.

Aging, then, is a process of unfavorable progressive change, usually correlated with the passage of time, becoming apparent after maturity, and terminating invariably in death of the individual.

It is interesting to note that the situation today in regard to a concept of aging is not too different from what it was 30 years ago. Dr. Raymond Pearl,[8] in his excellent little monograph entitled, *The Biology of Death*, summarized his thinking in this way:

"The problem of natural death has two aspects, one general, the other special. These may be stated in this way:

1. "Why do living things die? What is the meaning of death in the general philosophy of biology?

2. "Why do living things die *when* they do? What factors determine the duration of life in general and in particular, and what is the relative influence of each of these factors in producing the observed result?"

These two questions are fundamentally the same questions with which we are concerned today. Dr. Pearl goes on to list five biological generalizations concerning natural death, which again I will quote.

A. "There is an enormous variation in the duration of life, both intra and inter racially."

B. "There is no generally valid, orderly relationship between the average duration of life of the individuals composing a species and any other broad fact now known in their life history, or their structure, or their physiology." (He refers here to the usual attempts at correlation between metabolic rate and longevity, duration of fetal life and longevity, etc.)

C. "Natural death as distinguished from accidental death is preceded by definite structural and functional changes in the body." (We agree that there must be at least some structural and functional changes in aging but in essence we have failed to characterize them.)

D. "Natural death occurs normally and necessarily only in animals composed of many cells." (This statement is probably true in a qualified sense only. We now know that at least some Protozoa do age and die in the absence of periodical nuclear reorganization.)

E. "Life itself is a continuum. Natural death is a new thing which has appeared in the course of evolution. The somatic death of higher multicellular organisms is simply the price they pay for the privilege of enjoying those higher specializations of structure and function which have been added on as a side line to the main business of living things, which is to pass on in unbroken continuity the never-dimmed fire of life itself."

This was the status of affairs 30 years ago. It is remarkably unchanged. What I have tried to do is to draw a sharp line between problems of the aged and problems of the aging. Because of the rapid changes occurring in our population structure, we are urgently concerned with issues involving clinical management of the senile, social and economic ills of the elderly. The biology of aging—the study of the mechanism of aging is lagging seriously. Yet, in the long run, I strongly suspect that much of what we can do in at least the clinical care of the elderly will depend upon developments at the biological level. As Dr. Robert Moore

has aptly put it: "The biology of today is the medicine of tomorrow." This might be paraphrased to read, "The biological research on aging of today is the geriatrics of tomorrow."

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